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Report

Source Memory in the Rat

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Summary

Source memory is a representation of the origin (source) of information. When source information is bound together, it makes a memory episodic, allowing us to differentiate one event from another [1, 2]. Here, we asked whether rats remember the source of encoded information. Rats foraged for distinctive flavors of food that replenished (or failed to replenish) at its recently encountered location according to a source-information rule. To predict replenishment, rats needed to remember where they had encountered a preferred food type (chocolate) with self-generated (walking along a runway encountering chocolate) or experimenter-generated (placement of the rat at the chocolate site by an experimenter) cues. Three lines of evidence implicate the presence of source memory. First, rats selectively adjusted revisits to the chocolate location based on source information, under conditions in which familiarity of events could not produce successful performance. Second, source memory was dissociated from location memory by different decay rates. Third, temporary inactivation of the CA3 region of the hippocampus with lidocaine selectively eliminated source memory, suggesting that source memory is dependent upon an intact hippocampus. Development of an animal model of source memory may be valuable to probe the biological underpinnings of memory disorders marked by impairments in source memory.

Results and Discussion

People make judgments about the origin, or source, of information. Source memory refers to memories about the conditions under which a memory was acquired. Source information may include perceptual, contextual, temporal, affective, and other features that were present when the memory was formed. For example, if you search for your bike, you may initially be alarmed to discover the bike is missing, only to subsequently remember that today you arrived at work by car. In humans, source memory is involved in creating, remembering, and misremembering events. Source memory involves feature binding during encoding and access as well as evaluation processes during remembering. Consequently, episodic-memory tasks in people (which focus on our memories for unique personal events) involve source monitoring because they recruit attributions about the origin of mental experiences [3, 4].

Rats have a detailed representation of earlier episodes. This includes recollection of information [5, 6], memory of what, where, and when an earlier episode occurred [7–10], and the ability to retrieve information that was incidentally encoded and unexpectedly requested [11]. Thus, we asked whether rats remember the source of encoded information, namely by discriminating between encountering food following self-generated (walking along a runway encountering a distinctive food type) and experimenter-generated (placement at the site of a distinctive food type by an experimenter) events.

Rats foraged daily for food in an eight-arm radial maze. Upon first exposure, rats obtained their first opportunity to eat regular rat chow and a preferred food type, chocolate. The first opportunity to eat (first helpings of food) provided an opportunity to study food locations. After a delay, rats were returned to the maze to test their memory of the earlier episode (i.e., the location of a distinctive food type encountered at first helpings). To obtain their second opportunity to eat chow (second helpings), the rats needed to avoid revisiting locations where they obtained their first helpings earlier that same day because old locations no longer provided chow. A second helping of chocolate could be obtained by revisiting the same location that provided chocolate earlier, but the chocolate location replenished (or failed to replenish) according to a source-information rule. Consequently, obtaining second helpings of chocolate required the rat to not only remember what food they encountered and where they found it but also remember how they came to acquire it. An experimenter placement of the rat occurred during its first helpings of food: the rat was placed in front of one food trough, with food dispensed after the animal entered the trough. The source of chocolate in first helpings (i.e., the study phase) determined whether that location would replenish additional chocolate in second helpings (i.e., the test phase): if chocolate was obtained by placement feeding, then that location did not provide replenishment. By contrast, if chocolate was obtained by nonplacement feeding (i.e., a self-generated event in which the rat walked along the runway to obtain chocolate), then chocolate replenished at that location in second helpings. If rats have source memory, then they should be able to revisit the chocolate location at second helpings at a high rate in the replenishment condition (and limit revisits in the nonreplenishment condition). By contrast, if rats do not have source memory, then they should revisit the chocolate location at equivalent rates in replenishment and nonreplenishment conditions. An experimenter placement of the rat always occurred during their first helpings of food; the placement was either at a chow or at a chocolate location, which was randomly determined on each trial. The placement occurred equally often in each serial position of arm entries within first helpings, which was also randomly determined. Importantly, availability of chocolate during the second helpings depended on whether the rat obtained its first helpings of chocolate via self-generated or experimenter-generated events (see Supplemental Experimental Procedures available online.)

We asked whether rats selectively adjusted their revisits to the chocolate location based on their memories of the source of the encoded information (experiment 1). Experiments 2–4 converge on the conclusion that source memory in rats is episodic in nature by controlling for other explanations. We also asked whether source and location memory decay at different rates (experiment 3). Experiment 5 shows that a brain region thought to be critical for human episodic memory is also critical for this demonstration of source memory in rats.

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Experiment 1

To determine whether rats can distinguish between memories of self-generated and experimenter-generated events, we replenished chocolate in second helpings only after the rats had a self-generated encounter with chocolate. Thus, the rats needed to remember where they found chocolate during first helpings and the source by which it was acquired (self- or experimenter-generated). When replenishment in second helpings was predicted by self-generated, but not experimenter-generated, events, rats preferentially revisited the chocolate location when it was about to replenish [t(15) = 3.8, $p < 0.01$; Figure 1A]. Differential rates of revisiting chocolate locations were accomplished (in this and subsequent experiments) while rats accurately avoided revisits to depleted chow locations (see Table S1). The ability of rats to distinguish between memories of self-generated and experimenter-generated encounters of a distinctive food type is consistent with the hypothesis that rats have source memory.

Experiment 2

To determine whether rats used source memory flexibly rather than relying on memorized cues (e.g., handling, flavor, specific locations), we deprived the rats of a critical piece of information, namely the specific locations. We conducted a transfer test to a relatively novel room with different extramaze cues using the same rats. Importantly, because the rats did not have an opportunity to memorize the replenishment × encounter contingencies at locations in the novel room, rats in the novel room could not rely on memorization when deprived of extramaze cues from the initial room used in training. Accordingly, if rats had relied on memorization in experiment 1, then in the novel room they would visit the chocolate location at equivalent rates in replenishment and nonreplenishment conditions (failure to transfer to the novel room). By contrast, if rats in experiment 1 had learned a source-information rule, then in the novel room they would visit the chocolate location preferentially in the replenishment condition (successful transfer).

When first and second helpings occurred in a novel room, the rats preferentially revisited the chocolate location when it was about to replenish [t(15) = 3.0, $p < 0.01$; Figure 1B]. It is unlikely that successful transfer of performance to the novel room is due to a failure to discriminate the two rooms, because we independently verified that the two rooms are not substitutable; performance was severely disrupted when we conducted a study and test in different rooms. The fact that rats could differentiate between self-generated and experimenter-generated encounters of food in a novel context is consistent with the hypothesis that rats monitor source information.

Experiment 3

Next, we asked whether source memory and general memory for spatial locations decay at different rates. Different forgetting rates would suggest that source and location memory are distinct and dissociable. In humans, memory systems can be dissociated by different forgetting rates [12–14]. Thus, we examined source memory and location memory (as indexed by chow accuracy) using a wide range of delays (retention intervals 0–7 days) between first and second helpings of food; the delay in experiment 1 was ~4 min. Prior to collecting data using long retention intervals, we trained the rats with two chocolate-baited locations in each first-helping phase, one of which was obtained as an experimenter-generated event and one as a self-generated event (with order and location randomly determined). This refinement allowed us to obtain both a replenishment and a nonreplenishment condition each day, which more precisely matched the retention-interval challenges each day.

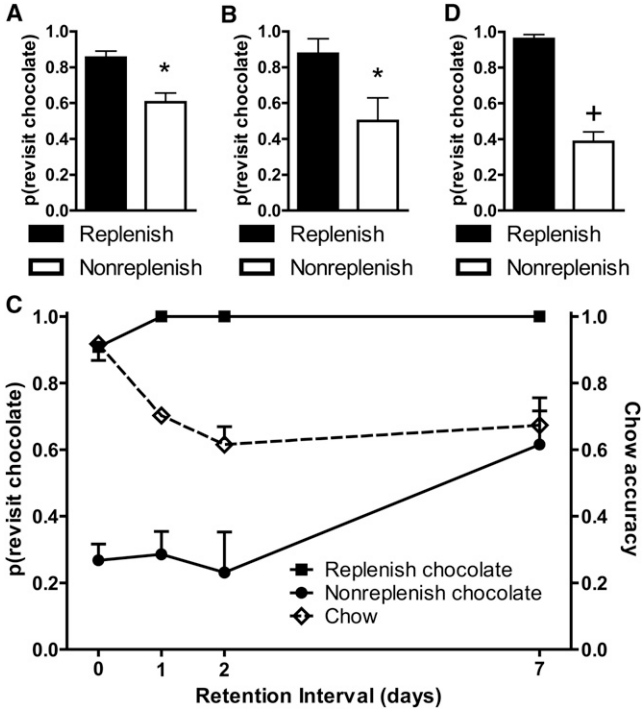

Figure 1. Source Memory Is Shown by a Higher Revisit Rate to the Replenishment Than the Nonreplenishment Chocolate Location

(A) Rats preferentially revisit the chocolate location when it is about to replenish in experiment 1. Self-generated (replenish) and experimenter-generated (nonreplenish) encounters with chocolate in study phases were presented in random order across sessions. *$p < 0.01$.

(B) Rats preferentially revisit the chocolate location when it is about to replenish in a novel context in experiment 2. Data come from one replenishment and one nonreplenishment trial. *$p < 0.01$.

(C) Source memory and location memory are dissociated by different decay rates across retention intervals of up to 7 days in experiment 3. Source-memory performance (indexed by more revisits to the replenishing chocolate location than to the nonreplenishing chocolate location, left axis) is unaffected by retention-interval challenges of up to 2 days, whereas location memory (indexed by chow accuracy, right axis) completes its decay over this same time period. Source-memory errors occur when the retention interval challenge is 7 days. At this time point, rats revisit the nonreplenish chocolate location. These incorrect revisits are likely due to source-memory failure because memory for the replenishing chocolate locations is intact at this time point.

(D) Rats encountered two chocolate locations per study phase, one self-generated and one experimenter-generated. When experimenter-generated, but not self-generated, events predicted replenishment in second helpings (i.e., a reversal of the arrangement used in experiments 1–3), rats preferentially revisited the chocolate location when it was about to replenish in experiment 4. Because the rats revisited replenishing chocolate locations at which they had recently been handled by an experimenter, these findings rule out expression of a place preference (i.e., avoidance of aversive locations). +$p < 0.0001$.

Data are mean with one SEM; the probability of a revisit to the chocolate location was calculated from the first four (A and B) or five (C and D) choices in test phases.

Revisits to the replenishment chocolate location (Figure 1C, squares) were uniformly high, even after a 7-day retention interval. By contrast, revisits to the nonreplenishment chocolate location (Figure 1C, circles) were uniformly low for

retention intervals of up to 2 days. The rats made source-memory errors when the retention interval was 7 days by increasing revisits to the nonreplenishment chocolate location. These are likely source-memory errors because they occur simultaneously without any loss of information about chocolate location. This observation is supported by the fact that the rats show retained accuracy in revisiting the replenishment chocolate location even after 7 days. This level of memory performance after a long retention interval in rats is remarkable and to our knowledge has not been documented in any other radial-maze experiment [15–17]. Source-memory decay is further dissociated from location memory as shown by the different rates of forgetting at shorter retention-interval challenges: chow accuracy (Figure 1C, diamonds) rapidly decayed during the shortest retention intervals, whereas virtually no errors in source memory were observed at these retention intervals. Importantly, by the longest retention interval, we documented a change in chocolate revisit rates: revisits to chocolate locations depended on both replenishment status and retention interval [interaction, $F(3,36) = 3.43$, $p < 0.05$], and as expected, revisits were also higher to replenishment than to nonreplenishment [$F(1,36) = 124.79$, $p < 0.0001$] and increased across retention intervals [$F(3,36) = 4.71$, $p < 0.01$].

Experiment 4

Although a higher revisit rate to replenishment chocolate location than to nonreplenishment chocolate location is consistent with source memory, an alternative hypothesis is that the rats were expressing a natural predisposition to avoid locations where aversive events recently occurred (i.e., handling by the experimenter). This possibility exists because in experiments 1–3, nonreplenishment was always at the location where the rat had recently been handled, raising the possibility that the experiment-generated events may have been mildly aversive. To test this nonsource memory hypothesis, we put the predictions of source memory and place preference in conflict by reversing the replenishment contingencies. If the results of earlier experiments were dependent on a predisposition to avoid aversive locations [18], then the revisit rates should now be higher at the nonreplenishment chocolate location. By contrast, if rats use source memory, then they should learn the new experimental contingency, in which case revisits should be higher at replenishment than nonreplenishment chocolate locations.

When experimenter-generated, but not self-generated, events predicted replenishment in second helpings, rats preferentially revisited the chocolate location when it was about to replenish [$t(12) = 9.6$, $p < 0.0001$; Figure 1D]. A preference for the replenishment chocolate location when replenishment occurred at either handled (experiment 4) or nonhandled (experiments 1–3) locations is consistent with the hypothesis that rats have source memory.

Experiment 5

The hippocampus is posited to be a critical processing center in source memory [2, 19–25] and is implicated in episodic-like memory in nonhuman animals [5–8, 11]. To test the hypothesis that our behavioral task requires source memory, we asked whether it was similarly hippocampal dependent. Specifically, if our behavioral task requires source memory and that memory is hippocampal dependent, then temporary inactivation of the hippocampus should impair the ability of rats to selectively revisit the replenishment chocolate location at a higher rate than the nonreplenishment chocolate location. The CA3 region of the hippocampus is postulated to mediate short-term elements of episodic memory [11, 26–28]. Therefore, stainless-steel guide cannulae were implanted bilaterally above the CA3 region of the hippocampus to enable us to temporarily inactive this region using infusions of lidocaine.

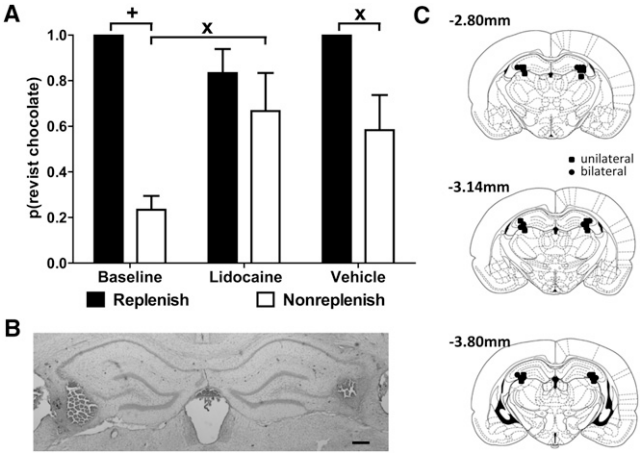

Figure 2. Temporary Inactivation of CA3 before Memory Storage Impairs Accuracy in Source-Memory Performance

(A) Source memory is indexed by a higher revisit rate to the replenishment than the nonreplenishment chocolate location, as shown in baseline. This difference was eliminated after lidocaine infusion. By contrast, after vehicle infusions, rats revisited the replenishment chocolate location at a higher rate than the nonreplenishment chocolate location, although the magnitude of this difference was attenuated relative to baseline. Data are mean with one SEM. The probability of a revisit to the chocolate location was calculated from the first five choices in test phases. Significant differences between bars connected by brackets are denoted by symbols: $\times p < 0.05$, $+p < 0.0001$.

(B) Representative example of Nissl-stained section showing bilateral infusion sites targeting the CA3 region of the hippocampus. Scale bar represents 500 μm.

(C) Coronal diagrams showing locations relative to bregma of infusion sites for all rats. Note that bilateral infusions spared CA1 and the dentate gyrus.

Baseline source-memory accuracy was reestablished after surgery [$t(5) = 7.9$, $p < 0.001$], demonstrating that surgical procedures alone did not disrupt performance. Next, to evaluate the impact of temporary inactivation of CA3, lidocaine or vehicle was infused before first helpings. The rats revisited the replenishment chocolate location at a higher rate than the nonreplenishment chocolate location during baseline (Figure 2A). This difference was eliminated after lidocaine infusion [$t(5) = 0.7$, $p > 0.05$; Figure 2A]. By contrast, after vehicle infusions, rats revisited the replenishment chocolate location at a higher rate than the nonreplenishment chocolate location [$t(5) = 2.7$, $p < 0.05$], although the magnitude of this difference was attenuated relative to baseline (Figure 2A). These observations are supported by a significant interaction of condition × replenishment status [$F(2,10) = 5.09$, $p < 0.05$]; revisit rates were higher to the replenishment than nonreplenishment location [$F(1,10) = 11.50$, $p < 0.05$] but did not differ across conditions [$F(2,10) = 3.21$, $p > 0.05$]. These results suggest that temporary inactivation of the hippocampus eliminated source-memory discrimination. Histological analysis verified that the center of the injection sites was concentrated in CA3 (Figures 2B and 2C). Performance did not differ in animals with clear bilateral placements in CA3 or placements where

CA3 was targeted primarily unilaterally, and these animals were pooled for statistical analyses.

Conclusions

Our findings suggest that rats monitor and remember the source of encoded information. We showed that source memory is dissociated from location memory and is hippocampal dependent, consistent with the hypothesis that source information is a feature of episodic memory. Judgments about the familiarity of recent events cannot explain preferential revisits to the replenishment chocolate location. First, chocolate replenishment was not predicted by the presence or absence of a recent placement because the placement always occurred during the rats' first helpings of food. Second, chocolate replenishment could not be predicted by the recency of placement; placement occurred equally often in each serial position of arm entries within first helpings (randomly determined).

To determine whether rats have source memory, we selected a source that included many salient features to distinguish self-generated and experimenter-generated events (e.g., tactile contact by an experimenter versus floor contact, different spatial trajectories, levels of effort, velocities, movements generated by self versus an experimenter, etc.). Although it is not known which source characteristics the rats may have used, the replenishment or nonreplenishment could not be predicted without source monitoring. The observation that rats possess source memory implies that source memory is evolutionarily quite ancient. Other approaches to study episodic memory in animals have focused on ecological problems faced by animals [29–31]. Source memory may be expected to confer survival benefit for the problems that rodents face in social transmission of food preferences [32–34].

Source memory in our behavioral procedure is remarkably long lasting. Rats remember the location baited with chocolate for at least 7 days without any apparent decay. Not only is the ability to avoid the nonreplenishment chocolate location intact without apparent decay for at least 2 days, the rats also likely remembered the nonreplenishment chocolate location after 7 days. By contrast, memory for chow locations, as defined by accuracy in avoiding revisits to chow locations, showed a decline that was complete after a 2-day retention interval. These results dissociate source memory from memory for location and flavor.

Errors of source memory occur in schizophrenia, posttraumatic stress disorder, depression, and Alzheimer's disease [2, 35]. Development of an animal model of source memory would be valuable for probing the neuroanatomical and molecular underpinnings of episodic-memory disorders. The ability to translate successfully from animals to humans will be improved by development of approaches that include modeling of the specific memory impairments observed in clinical populations [36], rather than general learning and memory assessments that are not specifically impaired. Moreover, understanding the functional organization of source memory will open opportunities to apply neurophysiological and genetic approaches to probe the neural and molecular underpinnings of memory disorders marked by impairments in source memory. These approaches can be used to understand changes in neuronal plasticity or neurotransmitter release that accompany source-memory disorders in future research. These targeted approaches may ultimately yield therapeutic approaches that improve memory with limited side effects.

Supplemental Information

Supplemental Information includes one table and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.01.023.

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References

1. Johnson, M.K., Hashtroudi, S., and Lindsay, D.S. (1993). Source monitoring. Psychol. Bull. *114*, 3–28.
2. Mitchell, K.J., and Johnson, M.K. (2009). Source monitoring 15 years later: what have we learned from fMRI about the neural mechanisms of source memory? Psychol. Bull. *135*, 638–677.
3. Johnson, M.K. (2005). The relation between source memory and episodic memory: comment on siedlecki et Al. (2005). Psychol. Aging *20*, 529–531.
4. McDuff, S.G.R., Frankel, H.C., and Norman, K.A. (2009). Multivoxel pattern analysis reveals increased memory targeting and reduced use of retrieved details during single-agenda source monitoring. J. Neurosci. *29*, 508–516.
5. Eacott, M.J., Easton, A., and Zinkivskay, A. (2005). Recollection in an episodic-like memory task in the rat. Learn. Mem. *12*, 221–223.
6. Fortin, N.J., Wright, S.P., and Eichenbaum, H. (2004). Recollection-like memory retrieval in rats is dependent on the hippocampus. Nature *431*, 188–191.
7. Eacott, M.J., and Norman, G. (2004). Integrated memory for object, place, and context in rats: a possible model of episodic-like memory? J. Neurosci. *24*, 1948–1953.
8. Ergorul, C., and Eichenbaum, H. (2004). The hippocampus and memory for "what," "where," and "when". Learn. Mem. *11*, 397–405.
9. Zhou, W., and Crystal, J.D. (2009). Evidence for remembering when events occurred in a rodent model of episodic memory. Proc. Natl. Acad. Sci. USA *106*, 9525–9529.
10. Zhou, W., and Crystal, J.D. (2011). Validation of a rodent model of episodic memory. Anim. Cogn. *14*, 325–340.
11. Zhou, W., Hohmann, A.G., and Crystal, J.D. (2012). Rats answer an unexpected question after incidental encoding. Curr. Biol. *22*, 1149–1153.
12. Tulving, E., Schacter, D.L., and Stark, H.A. (1982). Priming effects in word-fragment completion are independent of recognition memory. J. Exp. Psychol. Learn. Mem. Cogn. *8*, 336–342.
13. Schacter, D.L., and Tulving, E. (1994). Memory Systems (Cambridge, MA: MIT Press).
14. Mitchell, D.B. (2006). Nonconscious priming after 17 years: invulnerable implicit memory? Psychol. Sci. *17*, 925–929.
15. Beatty, W.W., and Shavalia, D.A. (1980). Spatial memory in rats: time course of working memory and effect of anesthetics. Behav. Neural Biol. *28*, 454–462.
16. Crystal, J.D., and Babb, S.J. (2008). Spatial memory in rats after 25 hours. Learn. Motiv. *39*, 278–284.
17. Roberts, W.A., Feeney, M.C., Macpherson, K., Petter, M., McMillan, N., and Musolino, E. (2008). Episodic-like memory in rats: is it based on when or how long ago? Science *320*, 113–115.
18. Schechter, M.D., and Calcagnetti, D.J. (1993). Trends in place preference conditioning with a cross-indexed bibliography; 1957–1991. Neurosci. Biobehav. Rev. *17*, 21–41.
19. Weis, S., Specht, K., Klaver, P., Tendolkar, I., Willmes, K., Ruhlmann, J., Elger, C.E., and Fernández, G. (2004). Process dissociation between contextual retrieval and item recognition. Neuroreport *15*, 2729–2733.
20. Eichenbaum, H., Yonelinas, A.P., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. Annu. Rev. Neurosci. *30*, 123–152.

21. Davachi, L., Mitchell, J.P., and Wagner, A.D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. Proc. Natl. Acad. Sci. USA *100*, 2157–2162.
22. Gold, J.J., Smith, C.N., Bayley, P.J., Shrager, Y., Brewer, J.B., Stark, C.E.L., Hopkins, R.O., and Squire, L.R. (2006). Item memory, source memory, and the medial temporal lobe: concordant findings from fMRI and memory-impaired patients. Proc. Natl. Acad. Sci. USA *103*, 9351–9356.
23. Corkin, S. (2002). What's new with the amnesic patient H.M.? Nat. Rev. Neurosci. *3*, 153–160.
24. Tulving, E., and Markowitsch, H.J. (1998). Episodic and declarative memory: role of the hippocampus. Hippocampus *8*, 198–204.
25. Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., and Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. Science *277*, 376–380.
26. Hunsaker, M.R., Lee, B., and Kesner, R.P. (2008). Evaluating the temporal context of episodic memory: the role of CA3 and CA1. Behav. Brain Res. *188*, 310–315.
27. Kesner, R.P., Hunsaker, M.R., and Warthen, M.W. (2008). The CA3 subregion of the hippocampus is critical for episodic memory processing by means of relational encoding in rats. Behav. Neurosci. *122*, 1217–1225.
28. Li, J.-S., and Chao, Y.-S. (2008). Electrolytic lesions of dorsal CA3 impair episodic-like memory in rats. Neurobiol. Learn. Mem. *89*, 192–198.
29. Clayton, N.S., and Dickinson, A. (1998). Episodic-like memory during cache recovery by scrub jays. Nature *395*, 272–274.
30. Ferkin, M.H., Combs, A., delBarco-Trillo, J., Pierce, A.A., and Franklin, S. (2008). Meadow voles, Microtus pennsylvanicus, have the capacity to recall the "what", "where", and "when" of a single past event. Anim. Cogn. *11*, 147–159.
31. Pahl, M., Zhu, H., Pix, W., Tautz, J., and Zhang, S. (2007). Circadian timed episodic-like memory - a bee knows what to do when, and also where. J. Exp. Biol. *210*, 3559–3567.
32. Bunsey, M., and Eichenbaum, H. (1995). Selective damage to the hippocampal region blocks long-term retention of a natural and nonspatial stimulus-stimulus association. Hippocampus *5*, 546–556.
33. Galef, B.G., Jr. (1986). Social interaction modifies learned aversions, sodium appetite, and both palatability and handling-time induced dietary preference in rats (Rattus norvegicus). J. Comp. Psychol. *100*, 432–439.
34. Galef, B.G., Jr., and Whiskin, E.E. (2000). Social influences on the amount of food eaten by Norway rats. Appetite *34*, 327–332.
35. Gallo, D.A., Chen, J.M., Wiseman, A.L., Schacter, D.L., and Budson, A.E. (2007). Retrieval monitoring and anosognosia in Alzheimer's disease. Neuropsychology *21*, 559–568.
36. Kimmelman, J., and London, A.J. (2011). Predicting harms and benefits in translational trials: ethics, evidence, and uncertainty. PLoS Med. *8*, e1001010.